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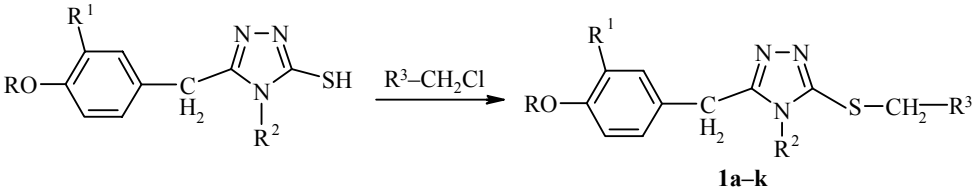
# SYNTHESIS OF SOME SUBSTITUTED 1,2,4-TRIAZOLE AND 1,3,4-THIADIAZOLE DERIVATIVES

**E. R. Dilanyan, T. R. Hovsepyan, and R. G. Melik-Ohanjanyan**

*New S-substituted 1,2,4-triazole and 1,3,4-thiadiazole derivatives have been prepared.*

**Keywords:** thiadiazole, thiosemicarbazide, triazole, cyclization.

We have already reported the synthesis of substituted 1,2,4-triazoles and 1,3,4-thiadiazoles [1], which have a broad spectrum of biological activity as it known from the literature data. Continuing a search for biologically active compounds of this type [2-5] and in an attempt to clarify the changes in the biological activity of these compounds upon replacing the free mercapto group with various substituents, we undertook the synthesis of a series of new S-substituted triazoles **1a-k** and thiadiazole **2**.




**1a–k**

**a**, **g** R = Et, **b**, **h** R = *i*-Pr, **c** R = Bu, **d** R = *i*-Bu, **e**, **f**, **i–k** R = Me, **a–d**, **f–h** $R^1$ = H, **e**, **i–k** $R^1$ = Br, **a–e** $R^2$ = Me, **f–k** $R^2$ = Ph; **a–i** $R^3$ = 3-Br–4-$MeOC_6H_3$, **j** $R^3$ = 3-Br-4-*i*-$BuOC_6H_3$, **k** $R^3$ = *i*-Bu

The starting 3,4-disubstituted 5-mercapto-1,2,4-triazoles were obtained in our laboratory by the cyclization of 1-[3-$R^1$-4-alkoxyphenylaceto]-4-$R^2$-thiosemicarbazides ($R^1$ = Br or H, $R^2$ = Me or Ph) in an alkaline medium with subsequent acidification by adding acetic acid [1]. The reaction of these products with 4-alkoxy-3-bromobenzyl chloride or isoamyl chloride in alkaline medium gave S-substituted triazoles **1a-k**. The potassium salt of 4-ethoxyphenylacetodithiocarbazic acid [5], which in the presence of concentrated sulfuric acid cyclizes to a 2-substituted 5-mercapto-1,3,4-thiadiazole, was used as the starting compound for the synthesis of S-substituted 1,3,4-thiadiazole **2**. The reaction of this mercapto derivative with 3-bromo-4-methoxybenzyl chloride gave compound **2**.

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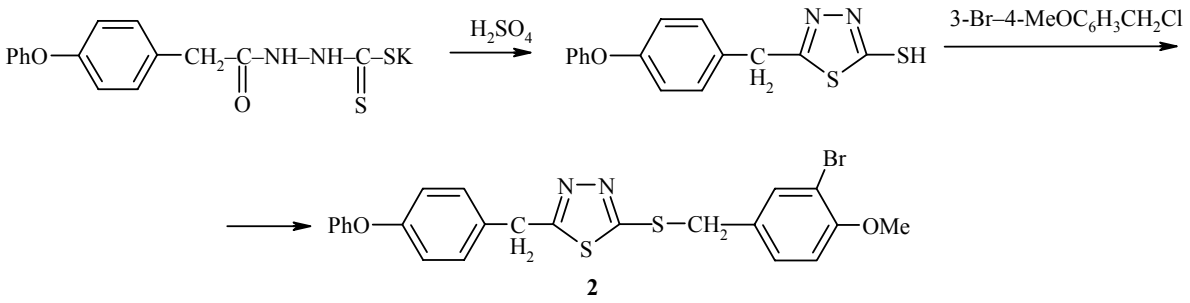
Institute of Fine Organic Chemistry, National Academy of Sciences of the Republic of Armenia, Yerevan 375014, Armenia; e-mail: melik@cornet.am. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1712-1715, November, 2008. Original article submitted June 20, 2005. Revised version submitted February 3, 2006.




**2**

TABLE 1. Physicochemical Characteristics of Products Synthesized

| Compound | Empirical formula | Found, % / Calculated, % | | | | mp, °C | $R_f$ | Yield, % |
|---|---|---|---|---|---|---|---|---|
| | | C | H | N | S | | | |
| **1a** | $C_{20}H_{22}BrN_3O_2S$ | 53.41 / 53.57 | 5.07 / 4.95 | 9.62 / 9.37 | 6.97 / 7.15 | 106-108 | 0.55 | 50.0 |
| **1b** | $C_{21}H_{24}BrN_3O_2S$ | 54.78 / 54.54 | 5.34 / 5.23 | 8.87 / 9.09 | 7.24 / 6.93 | 78-80 | 0.53 | 64.7 |
| **1c** | $C_{22}H_{26}BrN_3O_2S$ | 55.27 / 55.46 | 5.61 / 5.50 | 8.62 / 8.82 | 6.83 / 6.73 | 105-107 | 0.46 | 84.0 |
| **1d** | $C_{22}H_{26}BrN_3O_2S$ | 55.63 / 55.46 | 5.44 / 5.50 | 9.13 / 8.82 | 6.59 / 6.73 | 138-140 | 0.40 | 83.9 |
| **1e** | $C_{19}H_{19}Br_2N_3O_2S$ | 44.31 / 44.46 | 3.86 / 3.73 | 8.42 / 8.19 | 6.40 / 6.25 | 87-89 | 0.42 | 94.6 |
| **1f** | $C_{24}H_{22}BrN_3O_2S$ | 58.21 / 58.07 | 4.33 / 4.47 | 8.68 / 8.46 | 6.35 / 6.46 | 134-136 | 0.65 | 83.3 |
| **1g** | $C_{25}H_{24}BrN_3O_2S$ | 59.14 / 58.82 | 4.62 / 4.74 | 7.88 / 8.23 | 6.41 / 6.28 | 120-122 | 0.68 | 82.4 |
| **1h** | $C_{26}H_{26}BrN_3O_2S$ | 59.37 / 59.54 | 4.76 / 5.00 | 8.32 / 8.01 | 5.84 / 6.11 | 139-141 | 0.74 | 57.3 |
| **1i** | $C_{24}H_{21}Br_2N_3O_2S$ | 49.93 / 50.10 | 3.56 / 3.68 | 7.51 / 7.30 | 5.51 / 5.57 | 143-145 | 0.52 | 69.6 |
| **1j** | $C_{27}H_{27}Br_2N_3O_2S$ | 52.33 / 52.52 | 4.57 / 4.41 | 7.16 / 6.81 | 5.42 / 5.19 | 191-193 | 0.55 | 64.5 |
| **1k** | $C_{21}H_{24}BrN_3OS$ | 56.68 / 56.50 | 5.39 / 5.42 | 9.22 / 9.41 | 7.41 / 7.18 | 227-229 | 0.61 | 58.5 |
| **2** | $C_{19}H_{19}BrN_2O_2S_2$ | 50.47 / 50.55 | 4.11 / 4.24 | 6.43 / 6.21 | 13.85 / 14.21 | 77-79 | 0.76 | 88.8 |

All the products synthesized were chromatographically pure and identified using elemental analysis (Table 1) and $^1$H NMR (Table 2) and IR spectroscopy.

## EXPERIMENTAL

The $^1$H NMR spectra were taken on a Mercury-300 spectrometer at 300 MHz in DMSO-$d_6$. The IR spectra were taken on a UR-20 spectrometer for Vaseline mulls. The melting points were determined on a Boetius 72/2064 block. Thin-layer chromatography was carried out on Silufol UV-254 plates using 90:25:4 benzene-dioxane-acetic acid as the eluent with development by iodine vapor.

**3-[4-Alkoxy-3-bromo(or hydro)benzyl]-5-isoamyl(4-alkoxy-3-bromobenzyl)thio-4-methyl(phenyl)-1,2,4-triazoles 1a-k.** Corresponding 5-mercapto-1,2,4-triazole (10 mmol) was added to a warm solution of KOH (0.56 g, 10 mmol) in water (10 ml) and, then, 4-alkoxy-3-bromobenzyl chloride (10 mmol) or isoamyl chloride (synthesis of **1k**) was added with stirring. The mixture was heated at reflux for 1 h and then cooled. The crystalline precipitate was separated and recrystallized from methanol (Table 1).

TABLE 2. $^1$H NMR Spectra of Products Synthesized

| Com-pound | Chemical shifts, δ, ppm (SSCC, *J*, Hz) |
|---|---|
| **1a** | 1.38 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 3.11 (3H, s, N–$CH_3$); 3.82 (3H, s, $OCH_3$); 3.98 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 4.02 (2H, s, $CH_2$); 4.18 (2H, s, $SCH_2$); 6.76 (1H, d, *J* = 8.4, $C_6H_3$); 6.78 (2H, d, *J* = 8.6, $C_6H_4$); 7.04 (2H, d, *J* = 8.6, $C_6H_4$); 7.08 (1H, dd, *J* = 8.4, *J* = 2.2, $C_6H_3$); 7.44 (1H, d, *J* = 2.2, $C_6H_3$) |
| **1c** | 0.99 (3H, t, *J* = 7.4, $OCH_2CH_2CH_2C\underline{H}_3$); 1.49 (2H, qt, *J* = 7.4, *J* = 7.1, $OCH_2CH_2C\underline{H}_2CH_3$); 1.73 (2H, tt, *J* = 7.1, *J* = 6.3, $OCH_2C\underline{H}_2CH_2CH_3$); 3.11 (3H, s, N–$CH_3$); 3.82 (3H, s, $OCH_3$); 3.91 (2H, t, *J* = 6.3, $OC\underline{H}_2CH_2CH_2CH_3$); 4.02 (2H, s, $CH_2$); 4.18 (2H, s, $SCH_2$); 6.75 (1H, d, *J* = 8.4, $C_6H_3$); 6.78 (2H, d, *J* = 8.6, $C_6H_4$); 7.04 (2H, d, *J* = 8.6, $C_6H_4$); 7.07 (1H, dd, *J* = 8.4, *J* = 2.2, $C_6H_3$); 7.45 (1H, d, *J* = 2.2, $C_6H_3$) |
| **1d** | 1.02 (6H, d, *J* = 6.6, $OCH_2CH(C\underline{H}_3)_2$); 2.04 (1H, n, *J* = 6.6, $OCH_2C\underline{H}(CH_3)_2$); 3.11 (3H, s, N–$CH_3$); 3.68 (2H, d, *J* = 6.6, $OC\underline{H}_2CH(CH_3)_2$); 3.82 (3H, s, $OCH_3$); 4.03 (2H, s, $CH_2$); 4.18 (2H, s, $SCH_2$); 6.77 (1H, d, *J* = 8.4, $C_6H_3$); 6.79 (2H, d, *J* = 8.7, $C_6H_4$); 7.04 (2H, d, *J* = 8.7, $C_6H_4$); 7.08 (1H, dd, *J* = 8.4, *J* = 2.2, $C_6H_3$); 7.44 (1H, d, *J* = 2.2, $C_6H_3$) |
| **1e** | 3.16 (3H, s, N–$CH_3$); 3.82 (3H, s, $OCH_3$); 3.86 (3H, s, $OCH_3$); 4.04 (2H, s, $CH_2$); 4.19 (2H, s, $SCH_2$); 6.78 (1H, d, *J* = 8.4, $C_6H_3$); 6.93 (1H, d, *J* = 8.4, $C_6H_3$); 7.08 (2H, dd, *J* = 8.4, $C_6H_3$); 7.42 (1H, d, *J* = 2.2, $C_6H_3$); 7.45 (1H, d, *J* = 2.2, $C_6H_3$) |
| **1g** | 1.35 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 3.82 (3H, s, $OCH_3$); 3.90 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 3.95 (2H, s, $C\underline{H}_2$); 4.25 (2H, s, $SCH_2$); 6.70–7.55 (12H, m, Ar, Ph) |
| **2** | 1.39 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 3.86 (3H, s, $OCH_3$); 3.99 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 4.26 (2H, s, $CH_2$); 4.43 (2H, s, $SCH_2$); 6.79 (2H, d, *J* = 8.7, $C_6H_4$); 6.91 (1H, d, *J* = 8.4, $C_6H_3$); 7.16 (2H, d, *J* = 8.7, $C_6H_4$); 7.34 (1H, dd, *J* = 8.4, *J* = 2.3, $C_6H_3$); 7.56 (1H, d, *J* = 2.3, $C_6H_3$) |

IR spectra, $\nu_{max}$, $cm^{-1}$: **1b**) 1507 (C=N), **1c**) 1573 (C=N), **1h**) 1627 (C=N).

**5-(3-Bromo-4-methoxybenzyl)mercapto-2-(4-ethoxybenzyl)-1,3,4-thiadiazole (2)** was obtained analogously to the above procedure from 2-(4-ethoxy-5-mercaptobenzyl)-1,3,4-thiadiazole (2.21 g, 10 mmol) and 3-bromo-4-methoxybenzyl chloride (2.35 g, 10 mmol). IR spectrum, $\nu_{max}$, $cm^{-1}$: 1500 (C=N).

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